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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER

LAMBERTSON, DAVID A

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/544,045

Applicant(s)

SAUER ET AL.

Examiner

David A. Lambertson

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2004.
 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-49 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) ☒ Claim(s) 1-23 is/are allowed.
 6) ☒ Claim(s) 24-49 is/are rejected.
 7) ☐ Claim(s) _____ is/are objected to.
 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date _____.
 4) ☐ Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____.
 5) ☐ Notice of Informal Patent Application (PTO-152)
 6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed March 26, 2004.

Amendments were made to the claims.

Claims 1-49 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed January 2, 2004, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons set forth in the previous Office Action.**

Art Unit: 1636

Claims 24-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a variant/mutant Cre recombinase to produce site-specific recombination in a cell that contains recombination sites that are recognized by the variant/mutant recombinase, does not reasonably provide enablement for the use of any variant/mutant recombinase to produce site-specific recombination in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for reasons set forth in the previous Office Action.**

Response to Arguments Concerning Claim Rejections - 35 USC § 112

Applicant's arguments filed March 26, 2004 have been fully considered but they are not persuasive. With regard to rejection under the context of Written Description, Applicant provides the following grounds of traversal:

1. It is asserted that the recombinase being used in the rejected claims has already been established to mediate recombination at variant recombination sites. Furthermore, the claims are not directed to a recombinase composition, thus not only is it unnecessary to specify mutations that result in altered site specificity, it is also unnecessary to disclose a structure-function relationship for the recombinases to be used (see for example, page 13, second full paragraph of Applicant's arguments).
2. It is asserted that, on page 5 of the Office Action mailed January 2, 2004, the Office acquiesces that the instant specification properly discloses how to identify an Int with altered

Art Unit: 1636

recombination site specificity (see for example Applicant's arguments, page 13-14, bridging paragraph).

3. It is asserted that mutations in the enzymes need not be characterized in order to obtain recombination (see for example Applicant's arguments, page 14 top of the page).

4. It is asserted that the identification and characterization of Cre recombinase mutants shows the claimed methods have been reduced to practice, given the knowledge that other recombinases exist (see for example Applicant's arguments, page 14, last paragraph).

The arguments are not considered convincing for the following reasons:

1. While the assay to identify the variant recombinase (i.e., the allowable claims) would establish whether or not a given variant recombinase has the necessary functional activity to be used in the instantly rejected claims, this does not address the fact that only one such mutant is presently known (the 262 variant of Cre recombinase). An assay to identify a compound does not provide an adequate description of the compound itself. Rather, the assay merely establishes a functional requirement for the mutant recombinases, but still lacks the necessary structural component associated with the function, which is required to satisfy the written description requirement.

Applicant also argues that a disclosure of a representative number of variant recombinases or of a structure-function relationship to describe mutant recombinases that have altered recombination sites is unnecessary because the claims are not drawn to the recombinases themselves. While it is true that the claims are not directed to recombinases *per se*, the skilled artisan still needs to be in possession of the mutant recombinases to practice the claimed invention. Thus, omitting claims to the composition does not obviate the need to describe these

Art Unit: 1636

compositions if they are to be used in a further method. The fact of the matter is that, if the skilled artisan cannot even envision the recombinases to be used, the assay cannot be performed.

2. The assertion that the Office acquiesces to the description of Int mutants is unfounded.

Indeed, at the location indicated in the traversal, the Office states that the example of an Int recombinase exemplifies the lack of written description (see for example page 5, last paragraph of the Office Action mailed January 2, 2004).

3. The Office has not argued that the recombinases must be characterized in order to perform recombination. Rather, the Office has argued that the skilled artisan lacks the ability to envision the broad scope of recombinases that are claimed for use in the instantly rejected claims. The instant rejection is not a question as to *whether* a recombinase has altered site-specificity, but rather *which* recombinases have altered site specificity. Without an identification of the acceptable variant recombinases (i.e., a representative number of examples) or a structure-function relationship, the skilled artisan has no idea what recombinases to use in the instantly rejected claims.

4. As set forth in the previous Office Action, the skilled artisan cannot use the single example of a variant Cre recombinase (specifically, where the functional mutation is at amino acid 262) to make an analogous mutation in an unrelated recombinase such as Int or P1, etc. In other words, the skilled artisan cannot simply make a mutation at amino acid 262 in Int or P1, etc., and expect the recombinase to have an altered site specificity. Thus, the disclosure of a single working example is not demonstrative of the broad genus of variant recombinases claimed for use in the instantly rejected claims.

In conclusion, the current arguments do not present any evidence to suggest that the skilled artisan would be able to envision any of the variant recombinases claimed for use in the instantly rejected claims. The fact remains that an assay to identify such recombinases does not represent a description of the recombinases to be used. While the assay may uncover useful recombinases, until these recombinases are identified (or until such time that a structure-function relationship for such recombinases can be established) the skilled artisan cannot envision what recombinases will have the necessary altered site specificity required to practice the instantly rejected claims. Without an ability to envision the recombinases that are the functional element for practicing the instantly rejected claims, the claims cannot be performed. Indeed, the instantly rejected claims are directed to the use of hypothetical proteins that have not been discovered, let alone described in a structure-function capacity.

Applicant's arguments filed March 26, 2004 have been fully considered but they are not persuasive. With regard to the rejection in the context of Enablement, the following grounds of traversal are presented:

1. It is asserted that the instantly rejected claims are not reach through claims because the term "reach through" claims is generally reserved for prophetic disclosures claiming the exclusive right to the use of the patented item. It is asserted that in the instantly rejected claims, "downstream" or future compositions that may be identified via the use of the variant recombinases, are not being claimed. Rather, the instant claims are directed to a method for using an already identified variant recombinase to mediate recombination via recombination sites

Art Unit: 1636

that have already been found to be recombined via the variant recombinase (see for example Applicant's arguments, page 12, first paragraph).

2. It is asserted that the ability to translate a mutation in one recombinase to an entirely different recombinase is completely unnecessary in view of the claimed screening methods where the recombinase is identified. Additionally, the "unpredictability" asserted by the Office is not understood because there is no need to identify the mutations in the recombinases to be used in the instantly rejected claims.

The arguments are not considered persuasive for the following reasons:

1. The assertion that the instant claims are not "reach through" claims does not appear to be correct. Applicant correctly characterizes that "reach through" claims are generally reserved for "prophetic disclosures claiming the exclusive right to the use of the patented item." The instant claims describe two distinct assays: (1) an assay to identify a mutant recombinase, and (2) an assay to *use* an identified recombinase. In practicing the second assay, the skilled artisan would need to be in possession of the mutant recombinase. This mutant recombinase represents a "downstream" or future product, obtained from the first assay. However, aside from the Cre recombinase mutated at position 262, none of these products have been identified in the instant specification. Thus, in presenting claims for the use of the variant recombinases yet to be identified in the first assay, Applicant is prophetically claiming the exclusive use of an as yet identified item. The prophecy in the instant situation comes from the fact that the recombinases to be used in the instantly rejected claims are unknown. It is also asserted that the method of using the mutant recombinases only concerns already identified mutant recombinases. However, as set forth above, only one variant recombinase has been identified. The fact of the matter is

Art Unit: 1636

that the recombinases to be used in the instantly rejected claims are largely unknown, with the lone exception of the Cre mutant at position 262. Without knowledge of the elements to be used in the claimed invention (specifically, the functional element of the claimed invention), the skilled artisan cannot use the claimed invention.

2. The unpredictability of the invention stems from the fact that the skilled artisan has no idea what recombinases can be used in the claimed invention. The skilled artisan would need to identify the variant recombinases and their target sequences before being able to instantly use the recombinases. The instant specification provides no guidance as to the structure-function relationship of these variant recombinases, only a single functional (position 262) mutant of a single recombinase (Cre). As such, in order to use the variant recombinases, the skilled artisan would need to empirically determine which variant recombinases had altered site selection, and what sequences each variant was capable of recognizing. In the absence of an ability to translate the single mutation described in the instant specification from the Cre recombinase to any other recombinase (which Applicant considers unnecessary), the skilled artisan cannot make the recombinase that must be used in the instantly rejected claims. It is also noted that the ability to make and use is not equivalent of the ability to identify. Thus, the instant claims are directed to the use of hypothetical proteins, which have not and cannot be made given the teachings of both the instant specification and the state of the art at the time of filing.

In conclusion, the instantly rejected claims are still determined to be “reach through” claims, and thus do not satisfy the requirements of 35 USC 112, first paragraph. The instantly rejected claims are directed to the use of a composition (i.e., a recombinase) that is identified by a first method; however, the instant specification only provides a single example of the

Art Unit: 1636

composition to be used. The Office clearly recognizes that this example can be used in the instantly rejected invention, providing it as an allowable scope of enablement. However, the vast majority of variant recombinases claimed for use in the instantly rejected invention are unknown. As such, Applicant is laying claim to the exclusive use of a future/downstream product (i.e., one that has not been identified), the mutant recombinases; this is the definition of a "reach through" claim. Furthermore, because the scope of the products to be used in the instantly rejected claims is almost completely unknown, the ordinary skilled artisan would have to empirically determine both the nature of the variant recombinase, as well as its target sequence, before being able to practice the instant invention. As such, the previously applied enablement rejection is maintained in view of the current grounds of traversal.

Allowable Subject Matter

Claims 1-23 are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

Art Unit: 1636

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636



JAMES KETTER
PRIMARY EXAMINER